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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/562,627	12/22/2005	Mu-Hyeon Choe	428.1060	6450

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EXAMINER	
KOSSON, ROSANNE	
ART UNIT	PAPER NUMBER
1652	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/562,627	CHOE ET AL.	
	Examiner	Art Unit	
	Rosanne Kosson	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-47* is/are pending in the application.

4a) Of the above claim(s) *22-26,28,29,32-34,37,38 and 41-47* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21,27,30,31,35,36,39 and 40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 December 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/22/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicants' election with traverse of Group I, claims 21, 27, 30, 31, 35, 36, 39 and 40, drawn to a monomer that is a fusion protein comprising a functional domain that is an enzyme, an extension peptide containing a C residue and a binding domain, as well as to a homodimer of this monomer, in the replies filed on August 23, 2007, January 11, 2008 and April 28, 2008 is acknowledged. Applicants' elections of the species of the extension peptide of claim 21(iii)(a) and the fusion protein construction of antibody (binding domain)–extension peptide (linker)–functional domain (enzyme), N-terminally to C-terminally, are also acknowledged. No claims have been amended, canceled or added. Claims 22-26, 28, 29, 32-34, 37, 38 and 41-47 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to non-elected inventions, there being no allowable generic or linking claim. Claims 21, 27, 30, 31, 35, 36, 39 and 40 are withdrawn in part to the extent that they do not read on the elected invention, as being drawn to non-elected inventions. Accordingly, claims 21, 27, 30, 31, 35, 36, 39 and 40 are examined on the merits herewith to the extent that they read on the elected invention only.

In their traversal, Applicants assert that Choe et al. do not disclose an extension peptide that contains an uncoupled C, because the C3 connector has no C. Applicants assert that an examiner may elect to examine all of the claims in the application and that it would not be an undue burden to do so. Applicants assert that claims 24-26 should not be withdrawn because they 'refer back" to claim 21.

In reply, undue burden of search and examination is not a criterion in 371 applications, where unity of invention practice is applied. But, the instant application contains a large number of claims and a vast number of inventions, each of which requires a separate and distinct

search and examination. Each examiner has a limited amount of time to spend on one invention, and Applicants have not explained how searching and examining all of their many inventions can be accomplished in the amount of time allotted for one invention, particularly as Applicants have not provided a thorough discussion of the prior art for each claim and each invention. Further, the claim language is somewhat vague and all-encompassing, as conventional terms that recite molecules and structures known in the art have not been used. Thus, examining even one invention requires a considerable amount of time and review. Regarding claims 24-26, these claims recite the term "linker," which is not present in the elected invention. Therefore, these claims were withdrawn. As for Choe et al., again, the claim language is very broad, and the limits of the different portions in the fusion protein monomer are not clear. The C3 connector may not have a C residue. But, as previously discussed, the common technical feature among the different groups of inventions is a protein having a binding domain, linked to a C-containing extension peptide, linked to something else. Choe et al. disclose a fusion protein containing a binding domain (an Fab domain), an extension peptide that contains the light and heavy variable chains plus other intermediate sequences, such as the C3 domain, and something else (Pseudomonas exotoxin). The light and heavy variable chains contain C's. Therefore, Choe et al. disclose the common technical feature.

Regarding the species elections, as previously discussed, each species requires a separate and distinct search and examination. Thus, restriction is proper. Nevertheless, as also previously discussed, if a generic claim is found to be allowable, the corresponding species will be rejoined.

In view of the foregoing, the restriction requirement is maintained and is made final.

Claim Objections

Claims 27, 30, 31, 35, 36, 39 and 40 are objected to under 37 CFR 1.75(c) as being in improper form because they are improper multiple dependent claims. See MPEP § 608.01(n). In order to proceed with the examination, however, the claims have been interpreted as depending from claim 27 only. Appropriate correction is required.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 21, 27, 30, 31, 35, 36, 39 and 40 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Specifically, the claims recite two very large genera, a binding domain and a functional group domain. The specification recites on pp. 2-3 that the binding domain can be any antibody, any ligand that binds to a receptor or any receptor that binds to a ligand. But, the specification also discloses that the purpose of the claimed monomers and dimers is site-directed drug delivery and that the antibodies, ligands and receptors that work in the claimed invention are those that bind to cell-surface antigens, ligands or receptors, particularly those specific for mammalian tumor cells. That is, the binding domain cannot be any molecule that binds to any other molecule, i.e., any antibody, any ligand or any receptor but must be an antibody, ligand or receptor that binds to a cell-surface antigen. Also, the specification discloses that the functional group can be one of the types of molecules or

compositions listed in claim 27: an enzyme, a protein toxin, a virus that has a cationic tail for delivering DNA in gene therapy, a drug, a liposome or a biosensor (a term that is itself not described or exemplified in the specification). But, the functional group cannot be any composition or any molecule that has any function at all.. The specification makes it clear that the functional group is a therapeutic composition or molecule, while functional group encompasses any reactive chemical moiety (e.g., amino groups, carboxyl groups, aldehyde groups, thiol groups, phosphate groups, etc.), as well as any naturally occurring or synthetic molecule that participates in a biological or chemical reaction, whether or not the reaction is therapeutic. The disclosed species of the claimed genera are insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genera. A sufficient written description of a genus of molecules or compositions may be achieved by a recitation of structural features common to each member (species) of the genus, **which features constitute a substantial portion of each member of the genus**. The only recited features of the genera in these claims are functional limitations, i.e., the functions of binding to something for the binding domain and having a function for the functional group, which do not constitute a substantial structural portion of each species in the genus, as the structure is completely undefined and the specification does not define the remaining structural features necessary for members of the genus to be selected. Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

Consequently, there is no evidence that a sufficient number of representative species of this large genera were in the possession of the inventors at the time of filing. To satisfy the written description aspect of 35 U.S.C. 112, first paragraph, for a claimed genus of molecules, it must be clear that: (1) the identifying characteristics of the claimed molecules have been

disclosed, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these; and (2) a representative number of species within the genus must be disclosed. Because only a very limited number of species of the claimed genera are disclosed (three types of binding domains and six types of functional groups), the claims fail to satisfy the written description requirement.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 21, 27, 30, 31, 35, 36, 39 and 40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 27 is confusing because many of the compositions within the scope of the term "functional group" are not proteins. Claim 21, from which claim 27 depends, recites a fusion protein. Thus, the compositions listed in claim 27 should be proteins. Claim 21 encompasses the limitations of claim 27, and all the claims depend directly or indirectly from claim 21. Thus, all of the instant claims are indefinite.

Further, the claim recites the term "a virus for gene therapy, a compound with cationic tail for delivering DNA." It cannot be determined if Applicants mean to claim two types of functional groups with this term, a virus for gene therapy and a cationic gene therapy compound or just one group, i.e., the cationic tail describes the virus. Also, it is not clear what a compound with a cationic tail for delivering DNA is, rendering the claims indefinite, as this term is not

defined or explained in the specification. Further, the term "biosensor" is not defined or explained in the specification. It cannot be determined what Applicants mean by biosensor or what sorts of biosensors work in the claimed compositions (biosensors linked with a C-containing extension peptide to a binding domain). Clarification and appropriate correction, including the use of standard U.S. English and grammar (including articles), are required.

Claim 35 recites "one of the binding domain is an antibody." Presumably, Applicants mean "one of the binding domains." Again, the claims must be written in standard U.S. English. Appropriate correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 21, 27, 30, 31, 35, 36, 39 and 40 are rejected under 35 U.S.C. 102(b) as being anticipated by Choi et al. ("A divalent immunotoxin formed by the disulfide bond between hinge regions of Fab domain," Bull Korean Chem Soc 22(12):1361-1365, 2001), as evidenced by Ogata et al. ("Processing of Pseudomonas exotoxin by a cellular protease results in the generation of a 37,000-Da toxin fragment that is translocated to the cytosol," J Biol Chem 265(33):20678-20685, 1990).

Choi et al. disclose a fusion protein monomer containing, N-terminally, a binding domain that is an Fab fragment, the Fab fragment of the B3 antibody, which binds to superficial antigens that are abundant in many carcinomas (see Abstract). The Fab fragment is linked to an extension peptide containing a C that is adjacent to the Fab fragment and located in a hinge

region. The extension peptide is linked to a functional group that is an enzyme, a Pseudomonas exotoxin, PE38 (see Figs. 1 and 2, p. 1363). Ogata et al. disclose that Pseudomonas exotoxins are cytotoxic enzymes that catalyze the transfer of ADP-ribose to elongation factor 2 (see p. 20678, left col.). Thus, the fusion protein of Choi et al. is a site-directed anti-cancer drug, i.e., the binding moiety binds to a target molecule, a cancer cell surface antigen, and the functional group moiety (enzyme) acts on a cell attached to the target molecule.

Choi et al. disclose that antibody homodimers (homodimers of the fusion protein) may be formed, although the yield is low because the hydrophobic patches on the protein chains do not interact well. The monomers are formed in good yield, because the light and heavy chains have hydrophobic patches that do interact well. But, the yield of homodimers may be increased by raising the temperature of the medium in which the monomers are present (see p. 1364, left col.).

Regarding claims 39 and 40, the NaCl solution containing the monomer or dimer is a pharmaceutical composition (see p. 1364, left col.).

In view of the foregoing, a holding of anticipation is required.

Claims 21, 27, 30, 35, 36 and 39 are rejected under 35 U.S.C. 102(b) as being anticipated by Behringwerke AG (EP 501215 A2).

Behringwerke disclose a fusion protein monomer containing, N-terminally to C-terminally, a binding domain that is an Fab fragment, huTuMAK (human tumor-specific monoclonal antibody or a fragment thereof containing the V_L and V_H chains), a linker, L, and a functional domain that is an enzyme, β-glucuronidase (see p. 2, lines 1-15 and 54-55). The linker, Hinge 1, contains a C, encoded by TGT that is five amino acids away from the Fab

fragment (see p. 5, lines 35-45). The monomer can dimerize via the C residues in the V_H chain (see Figures Ma and Mc). Behringwerke do not disclose that the monomer can dimerize via the C residues in the linker, however any uncoupled cysteine residue is capable of participating in a disulfide bond and thus the cysteine residue of the linker meets all limitations of the instant claims.

Regarding claim 39, the monomer is a therapeutic composition in the category of antibody-enzyme conjugates (see p. 2, lines 9-41).

In view of the foregoing, a holding of anticipation is required.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rosanne Kosson whose telephone number is (571)272-2923. The examiner can normally be reached on Monday-Friday, 8:30-6:00, alternate Mondays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Nashaat Nashed can be reached on 571-272-0934. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Rosanne Kosson
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rk/2008-05-19

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